identical to SEQ ID NO:2" is found in the specification on page 7, lines 28-32, page 14 lines 15-25, page 15, lines 4-8 and page 16, lines 11-13. No new matter is added.

Support for the amendment to claim 41 is found in the specification on page 7, lines 28-32, page 10, lines 23-27, page 14, lines 20-32, and page 15, lines 1-3. No new matter is added.

Support for the amendment to claim 44 is found in the specification on page 10, lines 11-18, and page 14, lines 15-32, and in original claim 31 wherein it is stated that a high level of CHA4 expression is indicative of poor prognosis. Support for the change to "sequence encodes an amino acid sequence at least 95% identical to SEQ ID NO:2" is found in the specification on page 7, lines 28-32, page 14, lines 15-25, page 15, lines 4-8 and page 16, lines 11-13. No new matter is added.

Support for the amendment to claim 45 is found in the specification on page 10, lines 23-27, page14, lines 20-32, and page 15, lines 1-3. No new matter is added.

Support for newly added claims 48, and 49, is found in original claims 34 and 35, respectively.

Support for newly added claims 50 and 51 is found in original claims 38 and 39, respectively.

Objections to the Specification and Drawings

Priority

The Examiner objected to the priority claim because neither the first sentence of the specification nor the Application Data Sheet (ADS) contain a specific reference to the prior applications for which the application is claiming the benefit of priority. The specification has been amended by inserting a paragraph that refers to the priority applications in the first sentence of the specification.

The application was also objected to because the Examiner could not locate the references to the CHA4 sequence in the priority documents. The Applicants point out the CHA4 sequence, also referred to in the present specification as accession

number T32108 (see e.g. page 68, line 15) can be found in the priority documents as follows:

1. In USSN 09/525,993, filed March 15, 2000, reference to CHA4 can be found as reference to T32108 on page 2, of Table 13, line 40.

2. In USSN 09/493,444, filed January 28, 2000, reference to CHA4 can be found as reference to T32108 on page 1 of Table 10, line 19.

3. In USSN 09/453,850, filed December 2, 1999, reference to CHA4 can be found as reference to T32108 on page 1 of Table 10, line 19.

Thus, SEQ ID NO:1, CHA4 is supported by the earlier filing dates.

Drawings

The Examiner objected to the drawings because the sequences presented in Figures 1 and 2 did not contain appropriate SEQ ID NOs in the Figure or the figure legends. Furthermore, the Examiner objected to the drawings because the figure legend made reference to an underlined ATG start codon, which the Examiner could not locate.

The Drawings have been amended by providing a substitute sheet that includes a SEQ ID identifier in each of Figures 1 and 2.

The specification has been amended to correct the legend to Figure 1. The statement referring to an underlined ATG start codon has been removed.

The Applicants believe that these amendments address the Examiner's concerns and that the application is now in condition for allowance.

Specification

The disclosure was objected to because it contained an embedded hyperlink. The specification has now been amended to correct that oversight by eliminating the hyperlink. Those paragraphs that contained the hyperlink were replaced with paragraphs that deleted the hyperlink. No new matter is added.

The specification was also objected to because the Examiner alleged that the title was not descriptive of the elected invention. The title has now been amended to

refer specifically to methods for diagnosis and prognosis evaluation of breast or colorectal cancer. Reference to methods of screening for colorectal cancer modulators has been removed. No new matter is added.

Finally, the legend to Figure 1 has been amended to delete the statement "Start (ATG) and stop (TAG) codons are underlined". No new matter is added.

The Applicants believe that the amendments to the specification should address all of the Examiner's concerns and that the application is now in condition for allowance.

The Claim Rejections

Rejections under 35 U.S.C. §112, first paragraph

Enablement

Claims 32-47 are rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in such a way as to enable one skilled in the art to make and use the invention.

A. The Specification Enables Claims for the Diagnosis of Breast or colorectal Cancer.

The Examiner alleges that the data presented in Figures 3A-D do not appear to show differential expression between CHA4 in breast cancer and normal breast tissues, nor in normal colorectal tissue and colorectal cancer, because the normal and cancerous expression levels of CHA4 overlap. Therefore, the Examiner alleges that the evidence does not support the assertion that detecting the expression level of a gene comprising SEQ ID NO:1 allows for the diagnosis of breast cancer and/or colorectal cancer.

As a representative example of the prior art, the Examiner cites Beckman *et al.* U.S. Patent 5,516,658. The Examiner asserts that because Beckman *et al.* do not teach the use of Hek-L (CHA4) for the diagnosis of cancers, little is known in the prior art about the nature of the invention and so, the art is unpredictable.

Thus, the Examiner suggests that the enablement requirement has not been met because the art comprising the diagnosis of cancer from gene expression analysis is too unpredictable. The Applicants respectfully traverse the Examiner's rejection.

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the art as well as the predictability of the art. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is the less information needs to be explicitly stated in the specification MPEP 2164.03.

The Applicants point out that gene expression analysis is a means well known in the art for its efficacy in the diagnosis and prognosis evaluation of cancer. To support this point of view, the Applicants submit The National Cancer Institute Fact Sheet 5.18 as Exhibit 1. This fact sheet states that expression of certain genes function as useful markers for cancerous conditions, even though some marker levels can also be elevated in people with benign conditions. Despite the presence of markers in normal tissue, the fact sheet states that detection of tumor/cancer markers provides a useful tool for the dectection and diagnosis of some types of cancers when used along with x-rays or other tests.

The National Cancer Institute Fact Sheet also provides examples of some marker genes that are currently in use for cancer diagnosis. For example, prostate-specific antigen (PSA) which is present in low concentrations in the blood of all adult males may show elevated levels in the blood of men with benign prostate conditions, but also may be elevated in men with a malignant growth in the prostate. Nonetheless, PSA has become a useful diagnostic tool even though PSA levels alone do not allow doctors to distinguish absolutely between benign prostate conditions and cancer. In checking PSA levels, doctors generally look for trends, such as steadily increasing PSA levels in multiple tests over time, rather than focusing on a single elevated result.

Another tumor/cancer marker is prostatic acid phosphatase (PAP) which may be found at higher levels in some patients with prostate cancer, especially if the cancer has spread beyond the prostate. Elevated PAP levels have also been associated

with testicular cancer, leukemia, and non-Hodgkin's lymphoma, as well as noncancerous conditions such as Gaucher's disease, Paget's disease, osteoporosis, cirrhosis of the liver, pulmonary embolism, and hyperparathyroidism.

CA 125 is another useful tumor marker. Many women with ovarian cancer have elevated CA 125 levels. CA 125 levels may also be elevated by cancers of the uterus, cervix, pancreas, liver, colon, breast, lung, and digestive tract and by some noncancerous conditions such as endometriosis, pelvic inflammatory disease, peritonitis, pancreatitis, liver disease, and any condition that inflames the pleura. Nonetheless, CA 125 expression monitoring still provides a useful tool for diagnosis and prognosis evaluation of ovarian cancer.

Other tumor markers discussed on the National Cancer Institute Fact Sheet include: (a) Carcinoembryonic antigen (CEA) which is used primarily for monitoring colorectal cancer, (b) Alpha-fetoprotein (AFP) which can be elevated in the presence of either primary liver cancer or germ cell cancer, (c) Human chorionic gonadotropin (HCG) which can be used to screen for choriocarcinoma (a rare cancer of the uterus), (d) CA 19–9 which can be used in the diagnosis of colorectal cancer patients, (e) CA 15–3 which can be used to follow the course of treatment in women diagnosed with breast cancer, (f) CA 27–29 which may be used in conjunction with other procedures (such as mammograms and measurements of other tumor marker levels) to check for recurrence in women previously treated for stage II and stage III breast cancer, (g) Lactate dehydrogenase (LDH) which can be used to monitor treatment of some cancers, including testicular cancer, Ewing's sarcoma, non-Hodgkin's lymphoma, and some types of leukemia.

Thus, the diagnosis of cancer from gene expression analysis is a widely used and typically predictable field, the methods of which are well known in the art.

The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results of the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter

to which the claimed invention pertains, then there is predictability in the art (MPEP 2164.03).

The Applicants have shown that certain cancers can be identified by examining the expression patterns of SEQ ID NO:1. The data presented in Figures 3A-3D, show that some breast or colorectal cancers overexpress this sequence by comparison to many normal tissues, particularly normal breast and colorectal tissues. In particular, at least 17% of breast cancers have expression levels of CHA4 that are higher than the highest levels of expression seen in normal breast tissue. Therefore, some breast cancers can be identified by measuring expression levels of CHA4. Similarly, some colorectal cancers can be identified by measuring the expression of CHA4. Indeed, at least 86% of colorectal cancers can be identified by examining the expression of the CHA4 gene.

As noted on the National Cancer Institute Fact Sheet, "Tumor marker levels are not elevated in every person with cancer - especially in the early stages of the disease". Nonetheless, "Measurements of tumor marker levels can be useful - when used along with X-rays or other tests - in the detection and diagnosis of some types of cancer". Thus, it is not necessary that the invention be able to identify *all* breast cancers or *all* colorectal cancers, nor that it be absolutely determinative of breast or colorectal cancer.

The fact that the ranges for "normal" and "cancerous" tissue expression of CHA4 overlap in both breast and colon cancers is not relevant to the operability or usefulness of the invention. The Applicants have provided data showing that increased levels of CHA4 expression are correlated in a statistically significant manner with breast and/or colorectal cancer. As is typically practiced in the art, detection of CHA4 expression at a level indicative of breast or colorectal cancer will suggest that further tests be conducted to confirm the diagnosis of breast or colorectal cancer. Since such testing and evaluation is clearly routine in the art, undue experimentation is not necessary to practice the invention.

B. The Specification is Enabling for Prognosis Evaluation of Breast and Colorectal Cancer.

The Examiner alleges that the specification does not teach how expression of the claimed nucleic acids are predictive of prognosis. As indicated in the National Cancer Institute Fact Sheet, and as discussed above, the threshold level of expression needed for prognosis evaluation is a matter of optimization that is well within the ordinary skill in the art. The Applicants have shown that increased expression of CHA4 is indicative of colorectal cancer and/or breast cancer. Since increased expression is associated with cancer, it follows that higher levels of expression will correlate with a poorer prognosis evaluation for the patient. Indeed, this assertion finds support in original claim 31, wherein it is stated that a high level of CHA4 expression is indicative of poor prognosis.

The Applicants state that poor prognosis is associated with high levels of CHA4 expression, and show that increased expression is associated with breast or colorectal cancer. In light of these facts, the Examiner must provide reasoning or evidence that one of skill would not be able to practice the claimed invention without undue experimentation. In the absence of reasoning or evidence that refutes the above, the rejection is improper and should be withdrawn.

C. The Specification is Enabling for Sequence Variants Comprising SEQ ID NO:1.

The Examiner is concerned that the specification does not teach how to use all variants that are 75% identical with SEQ ID NO:1, since such variants might include variants such as splice variants etc that would be indicative of a different risk for cancer.

The claims have now been amended to recite "nucleic acids that encode an amino acid sequence at least 95% identical to SEQ ID NO:2". Thus, the claim encompasses variation as would be expected to occur naturally within the entire human population. The methodology for detecting allelic variants of SEQ ID NO:1 is well

known in the art, and such methods are referred to for example, on page 16, lines 10-15 of the specification.

D. Conclusion

To satisfy the enablement requirement, an application must contain sufficient information regarding the subject matter of the claims so as to enable one skilled in the art to make and use the claimed invention from the disclosure in the application coupled with information known in the art without undue experimentation. Indeed, a patent need not teach, and preferably omits that which is well known in the art (MPEP §2164.01).

The Applicants submit that they have identified a gene, CHA4, and shown that a high level of expression of the gene is statistically correlated with and breast or colorectal cancer. Thus, determining the expression level of CHA4 is a useful tool for the diagnosis and prognosis evaluation of breast cancer and colorectal cancer. The Applicants further submit that the field of cancer diagnosis by way of gene expression monitoring is a well established and well respected art. Therefore, the disclosure provided by the Applicants is sufficient, when combined with the teachings of the art, to permit one of skill to make and use the invention commensurate with the scope of the claims. Thus, the enablement rejection is improper and should be withdrawn.

Rejections under 35 U.S.C. §112, second paragraph

Claims 32-47 are also rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter the Applicants regard as their invention. In particular, the Examiner has rejected claims 32-43 over the recitation of "said gene(s)" when the expression of only one gene is being monitored. Claims 32-43 were also rejected because the Examiner alleges that it was unclear how the comparison would be used.

The Examiner has rejected claims 44-47 because the Examiner alleged that it was unclear how the expression analysis would be used to determine the prognosis of the individual.

Claim 32 has been amended to refer to expression of "a nucleic acid that encodes an amino acid sequence at least 95% identical to SEQ ID NO:2" and later refers to "said nucleic acid" rather than "said gene(s)". Claim 32 has been further amended to recite "wherein an increase in expression of said sequence in the first sample relative to the second sample provides a diagnosis of breast cancer or colorectal cancer in the first individual". It should now be clear how the comparison will be used.

Claims 33-43 are dependent on claim 32 and the defects in those claims are corrected by the amendments to claim 32.

Claim 44 has been amended to recite that a high level of expression of a nucleic acid that encodes an amino acid sequence at least 95% identical to SEQ ID NO:2 indicates a poor prognosis for the individual. It should now be clear that a high expression level is indicative of a poor prognosis.

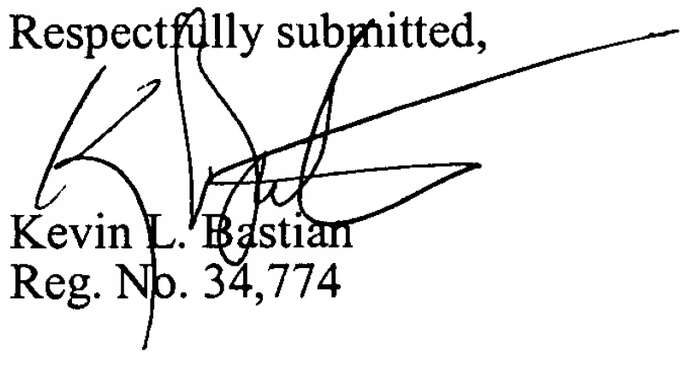
Claims 45-47 are dependent on claim 44 and the defects in those claims are corrected by the changes to claim 44.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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